1. Chang *et al.*, Appl Environ Microbiol 59: 3273-3279 (1993). This reference from nearly nine years ago discloses successful cloning and expression of a biosynthetic gene for aflatoxin biosynthesis, resulting in overproduction of a variety of aflatoxin intermediates.

2. Kennedy and Turner, Mol Gen Genet 253: 189-197 (1996). This reference from nearly six years ago discloses successful overexpression of a biosynthetic gene from *A. nidulans*, resulting in an increase in penicillin production.

3. Theilgaard *et al.*, Biotech and Bioeng 72: 379-388 (2001). This reference (after Applicants' priority date) discloses successful overexpression of a series of penicillin biosynthetic genes in *P. chrysogenum*, resulting in increased penicillin production.

4. Tag *et al.*, Mol Microbiol 38: 658-665 (2000). This reference (after Applicants' priority date) discloses successful constitutive expression of a fadA regulatory gene, upregulating a biosynthetic gene for penicillin and resulting in increased penicillin production.

These references, among others, suggest that the molecular tools for genetic modification are better developed than the Office Action suggests. These and similar tools are used to manipulate both biosynthetic and regulatory genes, and thus the unpredictability of the art may be overstated.

Written Description: Nature of the Invention and Teachings of the Specification

As emphasized by Applicants' representative, the claimed invention relates to methods for improving secondary metabolite expression in production fungi utilizing

particular classes of regulatory genes. Such genes may be known or novel; thus the claimed invention is not a "DNA invention".

The Declaration of Dr. Todd Milne was previously submitted to demonstrate that following the teachings of the specification results in successful practice of the claimed invention. For the Examiner's convenience, the following chart illustrates the teachings from the specification or the prior art that were used in the experiments described in Dr. Milne's Declaration.

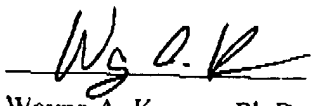
| **Milne Example** | **Specification Coordinates** |
|---|---|
| Example 1: Regulators of lovastatin | p. 19, l. 9; p. 21, l. 29; p. 22, l. 2; p. 16, 2d full paragraph (see also p.22, l. 10); p. 68, l. 12-p. 69, l. 28 |
| Example 2: Regulators of penicillin | p. 18, l. 27; p. 21, l. 29; p. 22, l. 2 (see also p. 22, l. 10; Lein (1986) |
| Example 3: Dominant positive mutation | p. 10, l. 1; p. 11, l. 8-12 |
| Example 4: Dominant negative mutation | p. 9, l. 30-31; p.11, l. 8-12 |
| Example 5: Dominant neomorphic mutation | p. 10, l. 3-6; p. 12, l. 10-12 |
| Example 6: Conditional expression | p. 13, l. 21-26 |
| Example 7: Small molecule modulator | p. 13, l. 13-14, 18-20 |

An examination of these teachings demonstrates that the specification, in view of the level of skill in the art teaches how to practice the invention without undue experimentation. According to Dr. Milne, the experiments described for each gene took an average of about 10.5 hours, including media preparation.

For the reasons discussed above, Applicants respectfully submit that given the level of skill in the art, the specification adequately enables the claimed invention.

Accordingly claims 1-28, 102 and 103 are now ready for allowance. If the Examiner believes that any discussion of this reply would be helpful, the Examiner is invited to call the undersigned attorney by telephone at 781-938-1805.

Respectfully submitted,



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